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Annual Research Review: Infant development, autism, and ADHD – early pathways to emerging disorders

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Background: Autism spectrum disorders (ASD) and attention deficit hyperactivity disorder (ADHD) are two of the most common neurodevelopmental disorders, with a high degree of co-occurrence. **Methods:** Prospective longitudinal studies of infants who later meet criteria for ASD or ADHD offer the opportunity to determine whether the two disorders share developmental pathways. **Results:** Prospective studies of younger siblings of children with autism have revealed a range of infant behavioral and neural markers associated with later diagnosis of ASD. Research on infants with later ADHD is less developed, but emerging evidence reveals a number of relations between infant measures and later symptoms of inattention and hyperactivity. **Conclusions:** We review this literature, highlighting points of convergence and divergence in the early pathways to ASD and ADHD. **Keywords:** Neurodevelopmental disorder, prediction, risk factors, developmental pathways, ADHD, autism spectrum disorders.

Introduction

ASD and ADHD are two of the most common neurodevelopmental disorders, each with an estimated prevalence of approximately 1–2% (Baird et al., 2006; Erskine et al., 2013). The vast majority of all research on these disorders takes place after diagnosis. However, symptoms of both ADHD and ASD likely emerge from a complex interaction between emerging neurodevelopmental vulnerabilities, and aspects of the child's prenatal and postnatal environment. While some symptoms may therefore reflect vulnerabilities related to genetic or environmental risk factors, others will be manifestations of compensatory processes or secondary 'cascading' effects following atypical interactions with the environment (Dennis et al., 2013; Johnson, Jones, & Gliga, in press). From a basic science perspective, after the clear emergence of symptoms it becomes hard to untangle these factors. Clinically, this may restrict us to treating symptoms, rather than the primary pathological processes that cause the disorder. Mapping how these common disorders unfold from birth is thus critical for understanding the chain of causal mechanisms leading to symptom emergence.

Over the past decade, there has been increasing interest in prospective studies of infants at high risk for ASD. The majority of these studies have focused on infants who have an older sibling with a diagnosis, and over 40 publications have now described potential early markers of later diagnosis of ASD in this population (for review, Jones, Gliga, Bedford, Charman, & Johnson, 2014); there are also reports from population studies (e.g. Bolton, Golding, Emond, & Steer, 2012) and other risk groups (e.g.

Cohen et al., 2013; Karmel et al., 2010). Research on infants with later ADHD is currently less developed. The high co-occurrence rates between these two disorders [approximately 20% of UK 7-year-old children with ASD meet criteria for ADHD, and vice versa (Russell, Rodgers, Ukoumunne, & Ford, 2014, note 1)] has raised the intriguing possibility that ASD and ADHD may share developmental pathways and risk factors. A range of emerging evidence for common ASD and ADHD endophenotypes (Rommelse et al., 2011), genetic (Ronald, Simonoff, Kuntsi, Asherson, & Plomin, 2008; Smoller, 2013) and environmental risk factors (Ronald, Pennell, & Whitehouse, 2011), and for moderate heritability (e.g. Ronald et al., 2008) has led some to suggest that the two conditions represent different manifestations of a common underlying disorder (Van der Meer et al., 2012).

Examining brain development prior to symptom emergence offers a new opportunity to investigate common or independent causal paths to ASD and ADHD symptomatology. Here, we review the literature on the emergence of ASD and ADHD in infancy to identify shared or unique variance in causal paths to symptomatology. We focus our review on the infancy period (prior to age 2 years), to identify the earliest expressions of risk. We have arranged the literature into several core domains, including brain size and structure, motor skills, sensory processing and perception, attention, temperament and regulation, and social interaction and communication. Within each section, we begin with a brief description of relevant concepts, and by briefly reviewing the key changes in that domain observed in children with ASD and ADHD – the common 'end point' for infancy work. Because infancy work in ASD is considerably more advanced, we next turn to work on infants with later emerging ASD, before moving on to ADHD and comparative

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studies. We include information from a range of different developmental populations including infants at familial risk, population cohort studies, and premature infants. While we structure our review by clinical outcome (ASD, ADHD), in light of the importance of considering the dimensional nature of childhood psychopathology (Coghill & Sonuga-Barke, 2012; Plomin, Haworth, & Davis, 2009), we extend the review to predictors of dimensional measures associated with ADHD or ASD traits. We note that studies of infants with later ASD have typically focused on relations with categorical clinical outcomes using expert 'clinical best estimate'. By contrast, studies of early ADHD have commonly used cut-points or clinical thresholds on dimensional measures of ADHD traits on population-normed screening scales, sometimes also combined with more direct clinical assessment and judgment. We return to the potential implications of this difference in outcome assessment is discussed in our conclusions.

After the literature review, we review the merits and challenges of studying neurodevelopmental disorders in infancy, and compare familial risk study designs to other study designs (e.g. large cohort studies; very preterm infants). In our conclusions, we argue for the importance of considering different models of the relation between infant measures and ASD and ADHD outcome (Figure 1), and propose terminology for greater precision in the way findings are described in the field (Table 1).

Review of the literature

Brain size and structure

Atypical brain volumes, cortical thickness, and connectivity have been observed in both ASD and ADHD. Rather than a trajectory of constant atypicality, complex nonlinearities have been described during development. In ASD, MRI-based measure-

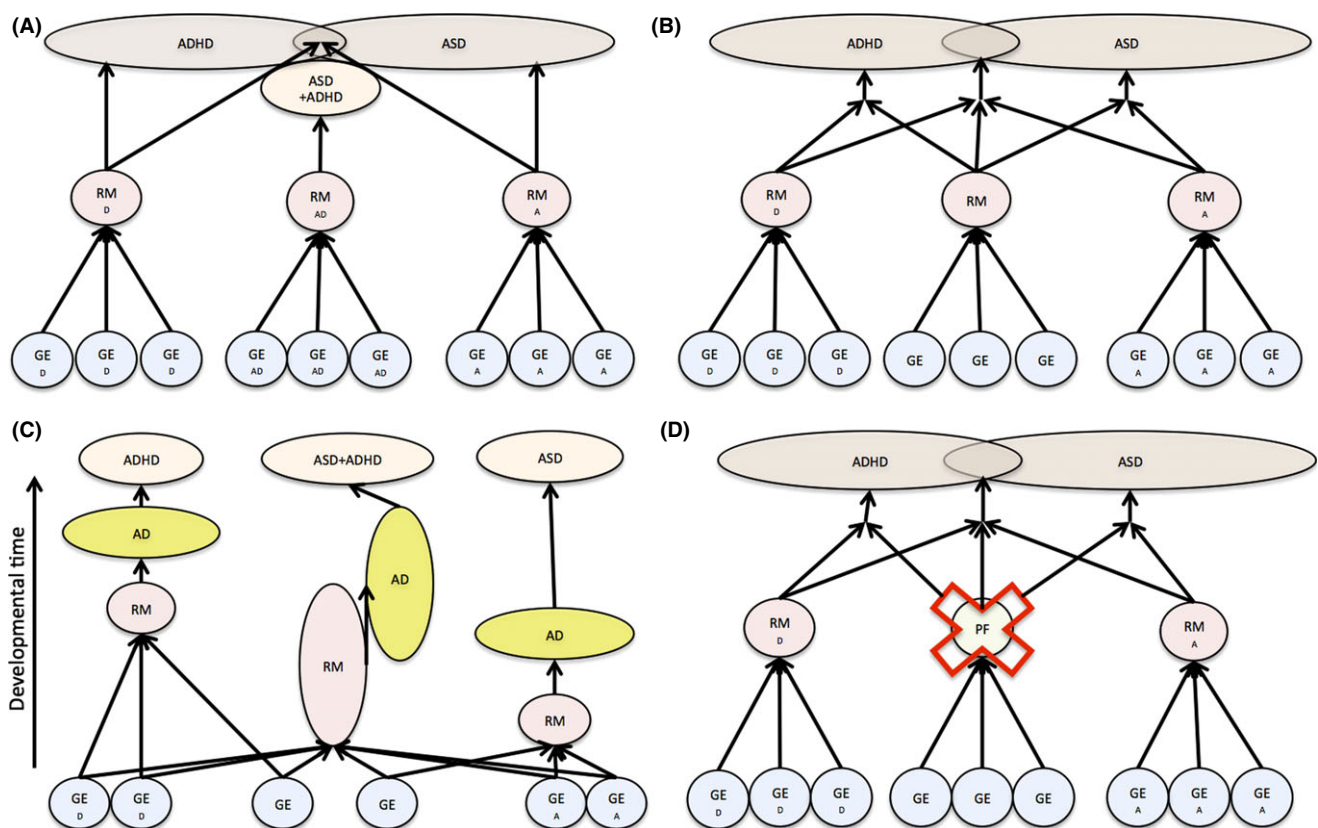


Figure 1 The four possible models of the developmental emergence of behavioral symptoms of ASD and ADHD. For simplicity, bidirectional interactions between genetic and environmental risk factors, intermediate phenotypes, and behavior over developmental time are not shown. (A) ASD and ADHD are associated with condition-specific risk markers; in addition, there are risk factors that specifically lead to comorbid ASD and ADHD. Here, some children with comorbid ASD and ADHD would represent a separate clinical group, while others would represent children who presented with risk factors of both ASD and ADHD. Testing this model in infancy requires studying the relation between early markers and later symptoms of ASD, ADHD, and their overlap. (B) Here, ASD and ADHD are caused by a combination of general risk markers, and condition-specific risk markers. (C) Here, common risk factors are activated at condition-specific points in development, but trigger common adaptive processes. Comorbidity is created by a longer period of activation. Condition-specific genetic and environmental factors affect the timing of expression of common risk markers. To test such models, it is critical to collect repeated measures of the same markers over time. (D) Risk factors for ASD and ADHD are condition-specific, but require the absence of condition-general protective factors to be expressed. Here, comorbidity simply results from the statistical overlap of the presence of risk factors for ASD and ADHD. Key: RM = Risk Marker; PF = Protective Factor; A = ASD; D = ADHD; AD = Adaptive response. GE = genetic and/or environmental risk factors

Table 1 Relating infant features to later outcome: Terminology. There are several ways in which particular patterns of cognitive, biological, or behavioral features in infancy may be related to later outcome of ASD or ADHD, each associated with different terminology. Different relations require different types of supporting evidence, and thus careful use of such terminology is critical to progression in the field

Term	Relation to later diagnosis
Potential marker	Group difference in the development of children with later ASD or ADHD
Marker/predictor	Marker with demonstration of predictive validity (e.g. sensitivity/specificity) in relation to categorical diagnosis
Precursor	Marker that indicates the approach of the disorder, i.e. is conceptually related to the core domains of difficulty (e.g. reduced social attention in infants with later ASD)
Antecedent	Marker that precedes diagnosis and has a causal relation to later symptoms; this may be demonstrated through the downstream effects of early intervention
Endophenotype	A heritable attribute that mediates between genetic and behavioral levels of explanation. (e.g. Gottesman & Gould, 2003)
Protective/compensatory factor	Marker that relates to later typical development across disorders, e.g. good executive functioning skills (Johnson, 2012)

ments of brain volume revealed overgrowth between 2 and 4 years of age followed by a deceleration in growth which results in adults with ASD having smaller brains than controls Courchesne, Campbell & Solso, 2011. From around the earliest diagnostic age to adulthood, ADHD is associated with smaller brain volumes (Hoogman et al., 2012; Krain & Castellanos, 2006). However, developmental changes are also observed later, such as cortical thinning in those individuals whose ADHD symptoms worsen from late childhood (Shaw et al., 2013). Various patterns of atypical structural connectivity have been described, with both hypo- and hyper-connectivity (depending on the brain structures studied and on the age of participants), in both ASD (reviewed in Uddin, Supekar, & Menon, 2013) and ADHD (Cao et al., 2013). As the relationship between brain function and structure is bidirectional (May, 2011), it is likely that some of these differences in brain structure are the consequence of years of atypical brain function, underlining the importance of studies of early development.

Early ASD. Most studies of brain size in ASD have relied on head circumference (HC) as a proxy measure. While many studies using this approach find early acceleration of head growth, a recent meta-

analysis indicates that the use of outdated population norms as a comparison group confounds much of this work (Raznahan et al., 2013). Studies using more recent population norms or recruiting matched controls have mixed results. Some find evidence for subtle increases in HC that are most apparent in the 2nd year of life (Dissanayake, Bui, Huggins, & Loesch, 2006; Hazlett et al., 2005); one study showed gender-specific patterns of either increased (boys) or decreased (girls) head circumference with no difference in rate of change (Surén et al., 2013); and another using a principle components approach found general overgrowth during the 1st year in one common factor related to variance in head size, weight, and length (Chawarska et al., 2011). There is some evidence that ASD has been associated with both higher rates of relative macrocephaly and relative microcephaly (HC related to body length), in newborns who later go on to autism (Grandgeorge, Lemonnier, & Jallot, 2013). Thus, data from head circumference measures present a mixed view on brain growth and its relation to somatic growth in autism. However, recent evidence that changes in head circumference may have predictive utility for later ASD when used in combination with other measures suggests that early accelerated head circumference should be further explored as a possible early identification mechanism for at least some children with ASD (Samango-Sprouse et al., 2014).

Importantly, a recent prospective neuroimaging study of infants at high familial risk corroborated observations of increased HC from 6 months of age with MRI measures of cerebral volumes. At both 12 to 15 and 18 to 24 months of age, infants with later ASD had larger brain volumes even when differences in body size were taken into account. Results also indicated that infants with later autism had greater volumes of extra-axial fluid at 6 to 9 months, which remained elevated at 12 to 15 and 18 to 24 months (Shen et al., 2013); this could also contribute to increased head circumference. One potential explanation for increased brain volume could be delayed pruning of excess connections. Consistent with this hypothesis, Wolff and colleagues (Wolff et al., 2012) found increased fractional anisotropy of white matter tracts (suggesting increased connectivity) within projection pathways connecting frontal and parietal areas to posterior cortical areas in 6-month-old infants that developed autism symptoms by 24 months of age.

Early ADHD. Slower increase in head circumference (HC) has been observed in retrospective studies of infants who later developed ADHD. Smaller head circumferences are apparent from 3 months of age and persist as far as 18 months of age (Gurevitz, Geva, Varon, & Leitner, 2012; Heinonen et al., 2011). Some report that head circumference is related to the severity of ADHD symptom scores (Heinonen et al., 2011), but this finding is not

universally observed (e.g. Stathis, O'Callaghan, Harvey, & Rogers, 1999). No anatomical abnormalities were observed in cranial ultrasound measures carried out on extremely low birth weight infants that later developed ADHD (O'Callaghan & Harvey, 1997), but a large-scale prospective study of infants with no birth complications did show a relationship between a shorter corpus callosum at 6 weeks of age and greater deficits in executive functioning at 4 years (Ghassabian et al., 2013). However, corpus callosum length did not relate to later Attention Deficit/Hyperactivity Problem Scores (Ghassabian et al., 2013). Most recently, using structural MRI in a population of very preterm infants, Bora, Pritchard, Chen, Inder, and Woodward (2014) document a relationship between reduced total cerebral tissue, particularly in the dorsal prefrontal region, and later persistent attention/hyperactivity problems.

General issues. Atypicalities in estimated and actual brain volumes appear to emerge during infancy in both ASD and ADHD. Although these findings require confirmation, there is converging evidence that, where confounds are dealt with, ASD is more often associated with increased HC or brain volumes and ADHD with decreased HC or volumes of particular structures. Very few studies have directly compared brain growths trajectories in ASD and ADHD. Gillberg and de Souza (2002) found no significant differences in head circumference at birth between children with ASD and ADHD, which suggest clear differences only appear later in development. Rommelse et al. (2011) compared early head circumference, height and weight over nine time points between birth and 18 months in 129 children with ASD and 59 children with non-ASD psychiatric disorders (ADHD, ODD, LD, regulation problems, developmental delay). No significant differences between groups were observed. Both groups showed increased growth in height that was not matched by head circumference with reference to population norms, such that by age 2 children were somewhat taller, thinner, and with proportionally smaller heads than in the general population. It is likely that, with including larger and more heterogeneous samples and frequent sampling more complex trajectories of change, with multiple points of acceleration and deceleration, will be revealed, which will not fit simple assumptions of linear growth.

Finally, for brain volume and structure data to contribute to describing causal mechanisms in the development of ASD and ADHD, it is crucial to understand which of a variety of factors, such as neuronal or glial cell number or size, number of synapses, white matter fascicle size or the size of the ventricles, most contribute to differences in brain volumes. Histological postmortem studies of brains from individuals with ASD have pointed to difference in both cellular number and size, sometimes specific to particular structures (e.g. more and larger pre-

frontal neurons; Bauman & Kemper, 2005). Increased brain volume could also reflect an early overproliferation of neural progenitors, as suggested by a subgroup of patients with ASD who share a mutation in CHD8 (Bernier et al., 2014). Filling this gap will be crucial for determining whether the patterns of atypical brain growth observed in adults are a cause or a consequence of atypical brain function.

Motor skills

Significant delays in achieving motor milestones such as crawling or walking are often 'red flags' for the presence of other disorders, and may have consequences for the development of skills in other domains. For example, independent locomotion is associated with improvements in spatial memory (Clearfield, 2004), and memory generalization (Herbert, Gross, & Hayne, 2007); reaching experience leads to greater understanding of goal-directed action (Sommerville, Woodward, & Needham, 2005). Thus, it is possible that early motor delays could form part of the trajectory to disruptions in other domains.

In ASD, atypicalities have been noted in postural control and in gross and fine motor coordination, movement patterns during locomotion and goal-directed motion (for review, Fournier, Hass, Naik, Lodha, & Cauraugh, 2010). Of note, these deficits are not only restricted to children with poor cognitive skills (Jansiewicz et al., 2006). Similarly, children with ADHD also show significantly poorer motor skills than children with typical development, such as in manual dexterity and balance (Pick, Halperin, Schwartz, & Newcorn, 1999) and reaching speed and accuracy in the absence of visual feedback (Eliasson, Rösblad, & Forssberg, 2004). There is a high degree of comorbidity between both ASD and ADHD and Developmental Coordination Disorder (e.g. Fliers et al., 2008; Kopp, Beckung, & Gillberg, 2010), and there is some evidence that motor deficits may be associated with shared risk for ASD and ADHD (Reiersen, Constantino, & Todd, 2008). Direct comparisons of children with ASD and ADHD suggest similar levels of motor impairment (Dewey, Cantell, & Crawford, 2007), and similar deficits in visual-motor integration (Englund, Decker, Allen, & Roberts, 2014). Thus, there is significant evidence for the presence of motor atypicalities in both ASD and ADHD.

Early ASD. Transient delays in early motor milestones have been widely reported in ASD. For example, displaying significant head lag when pulled to sit at 6 months is associated with later ASD diagnosis (Flanagan, Landa, Bhat, & Bauman, 2012). During free play sessions conducted at 6, 9, 12, and 14 months, four infants with later ASD diagnoses showed substantial delays in the emergence of new

postures, spent more time in less developmentally advanced postures (e.g. lying, sitting) and shifted posture less often (Nickel, Thatcher, Keller, Wozniak, & Iverson, 2013). Delays in performance on measures of fine and gross motor abilities are observed by the 2nd year in infants who go on to autism from high-risk families (Landa & Garrett-Mayer, 2006; LeBarton & Iverson, 2013; Ozonoff et al., 2010); similar delays were seen from 6 months in the ALSPAC longitudinal cohort (Bolton et al., 2012). These delays in skill acquisition may subtly disrupt developmental pathways through reducing an infant's opportunities for other types of learning. Indeed, decreases in fine motor skill in high-risk infants are correlated with later language development (LeBarton & Iverson, 2013), and infant oral and manual motor skills have been associated with teenage speech fluency in autism (Gernsbacher, Sauer, Geye, Schweigert, & Hill Goldsmith, 2008).

Atypicalities in other aspects of motor development have also been noted in early ASD. Studies of home videos taken in infancy also indicate atypicalities in early posture and tone (Adrien et al., 1993), asymmetric and unusual movements and reduced movement maturity at 6 to 9 months (Teitelbaum, Teitelbaum, Nye, Fryman, & Maurer, 1998; though see Ozonoff, Macari, et al., 2008; Ozonoff, Young, et al., 2008 for a critique of methodology and failure to replicate these findings); and atypical foot, arm, and global movements and less symmetric lying and walking postures as toddlers (Esposito, Venuti, Maestro, & Muratori, 2009). Prospective studies have also revealed differences in motor control; for example, a higher percentage of infants later diagnosed with ASD who spent time in neonatal intensive care showed abnormal upper extremity tone and asymmetric visual tracking at 1 month (Karmel et al., 2010). Interestingly, similar problems with visual tracking have been observed at 12 to 15 months in a case series of infants who later developed ASD (Bryson et al., 2007).

Early ADHD. Delays in gross motor milestones have also been measured from 3 months in infants who developed ADHD traits (Gurevitz et al., 2012); however, the ADHD group appeared to perform at the extremes, with some infants showing particularly *early* achievement of milestones (see also Jaspers et al., 2013). Although increased activity level is a characteristic feature of children with ADHD, a recent study found no relation between activity level coded from videotape at 12 months and ADHD at 7 years (Johnson et al., 2014).

Atypicalities have also been found in more subtle aspects of motor development in ADHD. For example, it is known that movement and visual attention are robustly coupled in typically developing young infants (e.g. Robertson, Bacher, & Huntington, 2001). As infants look at an object, ongoing motor activity decreases below baseline, before rebounding

and later surging above baseline as their gaze shifts away from the object. Movement suppression is likely coupled with increased activation of the parasympathetic nervous system, facilitating focused attention, and detailed processing of the stimulus. Increases in motor activity may release tonic inhibition of saccades exerted by the basal ganglia, increasing vulnerability to distraction, and facilitating eventual disengagement (Robertson et al., 2001). Friedman, Watamura, and Robertson (2005) examined the relation between motion-attention coupling at 1 and 3 months, and parent report of inattentiveness and hyperactivity at age 8 years. Inattentiveness at age 8 years was associated with less suppression of body movement at look onset, and greater rebound of movement following initial suppression at 3 months. The authors suggest that these patterns may reflect individual differences in the vulnerability of attention to disruption.

Other measurements of the complexity of movement during periods of quiet activity in very young infants have suggested atypicalities that may be related to later psychopathology. "General Movements" refer to the complex movements of trunk, head, arms, and legs that show different characteristic patterns during fetal life ('preterm'), at birth ('writhing'), and at around 3 to 4 months ('fidgety'; Einspieler & Prechtl, 2005), and have been linked to the integrity of the cortical subplate and its motor efferent connections in the periventricular white matter (Hadders-Algra, 2007). Healthy and preterm infants with mildly abnormal fidgety movements show higher levels of externalizing problems, distractibility, and aggression at 4–9 years, and this is associated ADHD with psychiatric comorbidity at age 9–12 (Hadders-Algra & Groothuis, 1999). Mildly abnormal general movements likely indicate compromised neurological functioning and are unlikely to be disorder-specific; indeed, Phagava et al. (2008) found reduced general movement optimality in home videos of infants later diagnosed with ASD.

General issues. Evidence suggests that delays in motor milestones may be a common feature of early ASD (e.g. Bolton et al., 2012) and ADHD (e.g. Gurevitz et al., 2012), though evidence in the latter case is more limited. What significance might delays in the attainment of early milestones have? Subtle disruptions to the timing of the achievement of particular core abilities may have negative consequences for development in other domains or may be a marker of more general developmental delay (see Discussion). For example, retrospective parent report of fine and gross motor skill in the early development of children with ASD is associated with later language skills in childhood (Gernsbacher et al., 2008), and motor skills and language skill are correlated in typical development (Alcock & Krawczyk, 2010), though this is likely confounded by the use of the same instrument to measure the two domains. However, rela-

tions between early milestones and continuous measures of outcome such as IQ in typical populations are generally very small and often clinically insignificant (e.g. Roze et al., 2010), indicating that any direct effect of variation in motor milestone attainment on other domains is likely very small. Further, delayed milestones have been observed across a wide range of conditions, suggesting they have limited specificity for any particular domain of atypicality (e.g. schizophrenia – Isohanni et al., 2001). Rather, current evidence is more consistent with the proposal that early transient motoric delays (or accelerations) may represent a general risk indicator for a range of conditions.

Sensory processing and perception

Over 90% of children with ASD present with sensory atypicalities, manifested as either hyper- or hypo-sensitivity (Leekam, Nieto, Libby, Wing, & Gould, 2007). Theories of autism explain sensory processing difficulties either as a result of improved discrimination, or poor filtering out, of incoming sensations (Markram & Markram, 2010; Mottron, Dawson, Soulières, Hubert, & Burack, 2006), or as difficulties with extracting higher level organization from sensory input (Happé & Frith, 2006). A replicated finding in ASD is that of superior visual search abilities. From as early as 2 years of age, toddlers with ASD more accurately detect visual targets in conjunction search displays (see Kaldy, Giserman, Carter, & Blaser, 2013 for review). In addition, brain imaging revealed enhanced activation of primary sensory cortices (Green et al., 2013). Sensory hyper-sensitivity has also been reported in ADHD, often as part of diagnosed Sensory Modulation Disorder (e.g. Lane, Reynolds, & Thacker, 2010). Tasks used to assess perceptual processing in ASD (e.g. visual search) lead to mixed results in ADHD (Maccari et al., 2012). Sensory gating paradigms [which measure event-related potentials to pairs of stimuli (e.g. clicks) with short within-pair and long interpair intervals], yield different findings in ASD and ADHD. A reduction in the amplitude of a midlatency component (P50) evoked by the second stimulus, thought to reflect the brain's ability to inhibit irrelevant sensory input is reduced in ADHD (Holstein et al., 2013). In contrast, it is the response to the first stimulus in the pair that differentiated participants with ASD and controls (Orekhova et al., 2008), suggesting different mechanisms underlying sensory atypicalities in the two disorder.

Early ASD. Few studies have directly examined sensory processing in infants with later emerging ASD. Overall performance on developmental measures of visual reception is reported to be typical at 6 months in infants that later develop ASD (e.g. Ozonoff et al., 2010). However, by 12 months infants who go on to ASD are more likely to show atypicalities in visual engagement with objects (e.g. using the

peripheral visual field during object manipulation; Ozonoff, Macari, et al., 2008; Ozonoff, Young, et al., 2008). Parental reports, as part of the Infant Behavior Questionnaire indicate that, from 6 months onward, infants with later ASD appear more reactive to sensory stimulation (Clifford, Hudry, Elsabbagh, Charman, & Johnson, 2013). In another study, including sensory-regulatory markers improved the accuracy of ASD screening at 12 months (Ben-Sasson, Soto, Martínez-Pedraza, & Carter, 2013). The inclusion of sensory symptoms in the DSM V criteria for ASD will likely increase focus on this area.

Early ADHD. Little is currently known about sensory processing in infants with later ADHD. However, diminished P50 sensory gating measured at 2.5 months was related to ADHD symptomatology (externalizing behavior, attentional problems) in addition to symptoms of anxiety and depression as assessed at 40 months (Hutchinson, Luca, Doyle, Roberts, & Anderson, 2013).

General issues. Sensory processing is still understudied in the development of ASD and ADHD. However, there is some evidence that both disorders may be characterized by early sensory issues. One question that future studies will have to address is whether sensory sensitivities reflect atypicalities of processing (e.g. tuning curves of sensory neurons or their thresholds), learning (e.g. to predict incoming stimulation), attention (e.g. selective attention), working memory (e.g. keeping track of the task relevant perceptual dimension), or regulation (e.g. of the response to incoming sensory stimulation). For example, there is still little consensus regarding what drives improved visual search abilities in ASD (e.g. Plaisted, O'Riordan, & Baron-Cohen, 1998), which could be related to increased arousal (Kaldy et al., 2013) or better perceptual discrimination (Plaisted et al., 1998). It is also unknown whether the hypo- or hyper- sensitivities described from early in life in ASD reflect stimulus-specific mechanisms (e.g. diminished reaction to hearing their name or any other linguistic information and hyper-sensitivity to unpredictable stimuli) or moment-to-moment fluctuations in attention. Fluctuations in sustained attention are also invoked to explain poor performance in search tasks in ADHD (as well as many other serial performance tasks; Maccari et al., 2012). Commonalities in perceptual processing may actually reflect commonalities in sustained attention abilities.

Attention

Attention is generally considered to comprise several different component processes (e.g. Colombo, 2001; Petersen & Posner, 2012). These include alertness (involving the brain stem and ascending noradrenergic and cholinergic pathways), exogenously driven

spatial attention (reliant on the posterior attention system, including the pulvinar, parietal lobe, and superior colliculus), attention to object features (involving occipital cortex and higher visual areas in inferior temporal cortex), and sustained or endogenous attention (associated with frontal areas such as the anterior cingulate, frontal eye fields, and dorsolateral prefrontal cortex). These systems have varied developmental courses (for review, Colombo, 2001), with alerting/arousal states typically maturing in early infancy and endogenous attention having a slower developmental course.

Atypicalities have been noted in all aspects of attention in ASD and ADHD, with mixed evidence for the specificity of particular deficits. Disruptions to alerting (the ability to attain and maintain an alert state) have been noted in both ASD and ADHD (Rommelse et al., 2011). For example, lapses in attention during continuous performance tasks are common in ADHD (for review Tamm et al., 2012) and have also been reported in individuals with ASD (e.g. Geurts & Embrechts, 2008). Spatial attention includes the ability to engage, disengage, and shift attention from a focus object, and is again implicated in both disorders. Here, some evidence suggests that children with ASD show relatively specific problems in disengaging attention (e.g. Landry & Bryson, 2004), although others find generally slowed orienting (Landry & Parker, 2013), and effects may be modulated by the social content of the stimuli (e.g. Chawarska, Volkmar, & Klin, 2010). Some evidence suggests that children with ADHD show slowed attention shifting that is not specifically related to a problem with disengagement (e.g. Klein, Raschke, & Brandenbusch, 2003), but a recent comparison of children with ASD and ADHD on a task that taps disengagement processes did not reveal group differences in behavior (Azadi et al., 2010). In the domain of feature attention (involving the processing of visual features and compounds), evidence indicates that young children with ASD show atypical feature attention that is particularly enhanced for faces (e.g. Chawarska & Shic, 2009; Webb et al., 2010, 2011). Less is known about feature attention in ADHD, although some aspects of differences in face processing may be relatively specific to ASD (Tye et al., 2013). Finally, sustained or endogenous control of attention refers to the ability to maintain attention over long periods, and inhibit response to distraction. Children with ADHD show well-documented deficits in sustained attention across a variety of contexts (e.g. Loo et al., 2009; Schoechlin & Engel, 2005). Direct comparisons of sustained attention in ASD and ADHD have variously indicated greater impairments in ADHD (e.g. Johnson et al., 2007); similar impairments but with a greater decrease over time in ADHD (Swaab-Barneveld et al., 2000); similar deficits but more impulsive behavior in ASD (Riccio & Reynolds, 2001); or broadly similar deficits across ASD, ADHD and

comorbid groups (Nydén et al., 2010). Toddlers with ASD may show more consistent reductions in sustained attention to naturalistic social stimuli (Chawarska, Macari, & Shic, 2012; Shic, Bradshaw, Klin, Scassellati, & Chawarska, 2011). Taken together, the balance of evidence suggests potential similarities in atypical sustained attention in ASD and ADHD (Rommelse et al., 2011).

Early ASD. Very little is known about attainment of the alert state in infants with later ASD, although differences in early modulation of attention by arousal level have been noted in premature infants with later ASD (Cohen et al., 2013). In the domain of attention shifting, slowed exogenously driven disengagement has been consistently noted at around 12 to 14 months in infants who go on to later ASD (Elison et al., 2013; Elsabbagh, Fernandes, et al., 2013; Zwaigenbaum et al., 2005). Similar behaviors are also seen during object exploration (slowed visual disengagement from the target of a reach; Sacrey, Bryson, & Zwaigenbaum, 2013), and in response to social stimuli such as a name call (Nadig et al., 2007). Such effects are typically absent at 6 months (Elsabbagh, Fernandes, et al., 2013; Nadig et al., 2007; Sacrey et al., 2013; Zwaigenbaum et al., 2005; though see Elison et al., 2013), suggesting that they emerge on a similar timescale to other early behavioral symptoms of autism. Interestingly, disengagement costs may be less apparent in toddlers with ASD (e.g. Chawarska, Klin, & Volkmar, 2003; Chawarska et al., 2010), suggesting that these effects may be transient; longitudinal follow-up of infants with early deficits will be critical to assess this possibility. Early concerns about vision and hearing in the ALSPAC cohort study (Bolton et al., 2012) may also reflect difficulty in shifting attention from the focus of interest to respond to a peripheral cue.

Few prospective infant studies have focused on aspects of sustained attention or attentional control, and results are mixed. In one study, *lower* distractibility from repetitive stimuli at 9 months was related to later variation in social and communication symptoms of ASD (Elsabbagh, Fernandes, et al., 2013). In contrast, during toy exploration, Sacrey et al. (2013) report that breaks in visual fixation prior to grasp are *more* common in infants who go on to ASD at 6 months than infants who go on to other outcomes; this effect declined with age. Chawarska, Macari, and Shic (2013) report that 6-month-old infants look less at a screen-based video with social content than other infants; this may reflect sustained attention difficulties, but could also reflect decreased interest in social events. Finally, parents prospectively judge their infants who went on to ASD as being less good at waiting at 9 and 18 months than other infants (Feldman et al., 2012). Taken together, this work suggests there may be subtle

atypicalities in sustained attention in early ASD, but a need for more systematic investigation.

Early ADHD. There is surprisingly little data on alerting, feature attention, orienting, and attention shifting in infants with later ADHD symptoms. One recent finding suggested that there may be early differences in endogenously driven orienting, as shorter duration of fixations in a screen-based task predicted poorer effortful control in early childhood (Papageorgiou et al., 2014); following up on such findings will be an important avenue for future work, as similar effects have also been noted in infants with later ASD (S. Wass, personal communication). As might be expected from work with older children, greater sustained attention in infancy is typically associated with reduced risk for later ADHD symptoms. Behaviorally defined focused attention during play-based tasks in the 1st year of life predicts variation in later processes relevant to ADHD (effortful control, attention, cognition, and hyperactivity and behavioral problems; Kochanska, Murray, & Harlan, 2000; Lawson & Ruff, 2004a,b). In one study, outcomes were particularly poor for low attentive children who also had higher negativity, suggesting that examining combinations of risk factors will be important (Lawson & Ruff, 2004b). This range of evidence suggests that lack of focused attention during toy play in infancy is related to ADHD-type behaviors in the preschool years. Similarly, in a group of typically developing infants, greater distractibility in infancy was related to common polymorphisms associated with increased risk of ADHD (Holmboe et al., 2010), and better spatial conflict resolution, but *worse* effortful control at age 2 years (Holmboe et al., 2010). Adding measures of intraindividual variability in reaction time to such tasks will be important, given that increased variability is a more robust feature of ADHD in childhood than changes in mean reaction time (Kofler et al., 2013). Further, most current research on this topic looks at outcomes only indirectly associated with ADHD diagnosis.

General issues. The literatures on early ASD and early ADHD have generally focused on different components of attention, making direct comparisons difficult. Studies of early ASD have typically focused on examining spatial orienting (e.g. Elsabbagh, Fernandes, et al. 2013; Elsabbagh, Gliga, et al. 2013; Nadig et al., 2007). Although current work shows a clear pattern of early emerging atypicalities in exogenously and endogenously driven disengagement at 12 to 14 months in infants with later ASD, similar phenotypes have yet to be examined in infants with later ADHD. Similarly, longitudinal studies examining later variability in ADHD-relevant domains have commonly focused on early, sustained attention, as this is a robust hallmark of later ADHD (e.g. Lawson & Ruff, 2004a). The few studies of related measures

in ASD have yielded mixed results, but suggest that subtle atypicalities may also be present early in the development of this disorder.

It should not be assumed that the very early manifestations of attention deficits in infants who later develop ASD or ADHD will necessarily resemble the deficits seen in older children. Rather, even subtle and transient impairments may have significant developmental consequences. This is perhaps illustrated by disengagement effects, which appear to be much clearer at 12 months (e.g. Elsabbagh, Fernandes, et al. 2013; Elsabbagh, Gliga, et al. 2013) than in later development (e.g. Landry & Parker, 2013). However, other aspects of attention may be more consistent between infant and toddler samples, such as sustained attention to social scenes (e.g. Chawarska et al., 2012; Shic et al., 2011). Further, it will be important to examine how the attention atypicalities seen in infants with later ASD relate to comorbid ADHD symptoms. Long-term follow-up of cohorts of at-risk infants at ages at which ADHD can be more readily diagnosed will be critical to answering such questions. Finally, incorporating other psychophysiological or imaging measures (such as heart-rate, motion, or EEG) into assessments of attention in at-risk groups may identify more subtle underlying atypicalities that precede or underlie behavioral changes in attention, and may indicate whether apparently similar deficits have distinct underlying causes.

Temperament and regulation

Temperament has been defined as “constitutionally-based individual differences in reactivity and self-regulation, as observed in the domains of emotionality, motor activity, and attention” (Rothbart, Posner, & Kieras, 2008); Rothbart’s influential model (used in many studies on ASD/ADHD) separates temperament into effortful control/self-regulation, extraversion/surgency, and reactivity/negative affectivity (Rothbart, Ahadi, & Evans, 2000). Average scores on core temperament domains vary in children diagnosed with ASD or ADHD. For example, children with ASD often exhibit reduced effortful control and higher negativity (e.g. Konstantareas & Stewart, 2006); and similar patterns are seen in children with ADHD (e.g. Nigg, Goldsmith, & Sachek, 2004). The temperamental profiles of children with diagnoses of ASD and ADHD thus appear broadly similar in these domains. Where direct comparisons of effortful control and negativity have been made, few differences between ADHD and ASD groups are observed (e.g. Anckarsäter et al., 2006). Rommelse et al. (2011) review temperament as one of the domains that may represent a shared endophenotype between ASD and ADHD. However, reduced levels of approach or surgency may be relatively specific to children with ASD (Schwartz et al., 2009), as ADHD is more often associated with higher levels of approach or surgency that are

potentially related to impulsivity (Martel & Nigg, 2006). Further, a recent comparative study found that group differences in temperament and character only overlapped on two of seven domains in groups with ASD and ADHD (Sizoo, van der Gaag, & van den Brink, 2014), challenging the hypothesis that this represents a common endophenotype. Thus, the three factors underlying temperament in infancy may have different degrees of specificity to a later ASD or ADHD diagnosis.

Early ASD. Several studies have examined parent reports of temperament in infants with a later diagnosis of ASD. By age 24 months, children with later ASD show greater negative affect than other toddlers; this is less apparent at younger ages (e.g. Clifford et al., 2013; Zwaigenbaum et al., 2005). Positivity appears reduced by 12 months (Clifford et al., 2013; Zwaigenbaum et al., 2005) and remains low at 24 months (Del Rosario, Gillespie-Lynch, Johnson, Sigman, & Hutman, 2014; Garon et al., 2009) in infants with later ASD. These general patterns are consistent with those seen in older, diagnosed children. Effects seem to broadly increase in severity and scope with age, possibly suggesting that these temperament changes relate to the emergence of other behavioral symptoms. Indeed, Del Rosario et al. (2014) observed that infants with later ASD showed initially higher levels of approach and adaptability, and lower activity level, at 6 and 12 months than controls. However, by age 2 years, these children were showing *lower* approach and adaptability, and no differences in activity level, broadly consistent with work with clinically referred samples. Although these effects have not been reported in other cohorts, they suggest that the temperament patterns that are most likely to represent causal or early infancy risk factors do not necessarily resemble those seen in older, diagnosed children.

Self-regulation/effortful control also appears generally reduced in the 2nd year of life in infants with later ASD (Clifford et al., 2013; Del Rosario et al., 2014; Garon et al., 2009; Zwaigenbaum et al., 2005). Across studies, this effect was not apparent earlier in development. Similarly, temperament differences did not emerge as significant predictors of later ASD until 2 years of life in the ALSPAC longitudinal cohort (Bolton et al., 2012).

Alternatively, examining earlier precursors of regulatory control may reveal important group differences. Indeed, atypical neonatal auditory brainstem responses and atypical patterns of arousal-modulated attention at 4 months predict later autism in preterm infants (Cohen et al., 2013; Karmel et al., 2010); these behaviors have been linked to later self-regulatory capacity (Geva & Feldman, 2008). Other basic early regulatory behaviors that may be related to later effortful control difficulties are feeding and sleeping; disruptions to both have been reported in

early ASD (Bolton et al., 2012; though see Jaspers et al., 2013). Mapping the longitudinal relations between early brainstem-related physiological regulation, frontal cortex development and effortful control of attention and emotion will provide insight into the roots of effortful control atypicalities in children with ASD.

Early ADHD. Temperament atypicalities are apparent from 6 months in infants with high levels of ADHD symptoms in preschool (Arnett, Macdonald, & Pennington, 2013); specifically, infants with later ADHD symptoms were characterized as showing higher activity level, less adaptability, reduced approach, negative mood, and high intensity. A retrospective chart review of children with ADHD or ASD indicated that later ADHD was predicted by early attention and hyperactivity problems, and absence of parent-reported positive behaviors in toddlerhood; conversely, ASD was predicted by social problems in toddlerhood (Jaspers et al., 2013). In another population cohort, difficult temperament was more commonly reported by parents of 9- and 18-month-old infants who later developed ADHD, with only 62% and 47% characterized as 'easy' (vs. 90%/81% of the control group; Gurevitz et al., 2012). Taken together, this work suggests that temperament profiles in infants who go on to ADHD may be different to those in infants who go on to ASD. In the two studies that used very similar measures (Arnett et al., 2013; Del Rosario et al., 2014), 6-month olds with later ASD showed better adaptability and more approach (Del Rosario et al., 2014), while 6-month olds with later ADHD showed lower adaptability and lower approach (Arnett et al., 2013). Temperamental risk factors for ASD and ADHD seem to be different in very early development.

Atypicalities in physiological regulatory processes may also be apparent in early ADHD. For example, sleep difficulties predict later diagnosis of ADHD (O'Callaghan et al., 2010; Thunström, 2002; there is less evidence to support this for ASD – Jaspers et al., 2013). Gurevitz et al. (2012) also found poorer sleep regulation at 3 months in infants later diagnosed with ADHD, and Geva, Yaron, and Kuint (2013) found that poor neonatal sleep predicts later attention orienting and distractibility. Interestingly, increased prevalence of 'regulatory disorder' (excessive crying with feeding and sleeping problems) in infancy is associated with ADHD, but only in the presence of the DRD4 -7 risk allele (Becker et al., 2010). Consistency of such patterns across ASD and ADHD raises the possibility that physiological regulatory difficulties represent general risk factors for later psychopathology.

General issues. An open question is the degree to which temperament differences in infants with later ASD or ADHD reflect the early manifestation of behavioral symptoms of the disorder (which would

be expected to be condition-specific, emerge over time, and be similar in form to temperamental differences seen in older children); or whether different temperamental profiles represent general risk, or differential susceptibility factors (which would not be condition-specific, would be apparent very early in development, and may take a different form to differences seen in older children). The work reviewed above provides evidence consistent with a certain degree of condition specificity of some temperament constructs (Arnett et al., 2013; Del Rosario et al., 2014; Jaspers et al., 2013). Temperament patterns seen in toddlers with later ASD or ADHD also seem to broadly resemble those seen in children with a diagnosis, although this is not necessarily the case in infancy (e.g. infants with later ASD show *reduced* approach in toddlerhood, but *greater* approach in infancy; Arnett et al., 2013; Del Rosario et al., 2014). Finally, longitudinal datasets from infants who later develop ASD suggest that differences from typically developing controls are more widespread and more pronounced in older infants (e.g. Clifford et al., 2013; Del Rosario et al., 2014; Zwaigenbaum et al., 2005), a finding that has not been explicitly tested for ADHD. Thus, it is likely that at least some temperamental differences seen in toddlers with later ASD/ADHD result from changes in other behavioral symptoms.

Finally, given that temperamental dimensions interact with each other during development, their predictive value will depend on a comprehensive characterization at multiple points during development. For example, the association between regulatory disorder in infancy and ADHD in childhood is moderated by the presence of the DRD4-7 risk allele (Becker et al., 2010).

Social interaction & communication

Impairments in social communication are a core part of the diagnostic criteria of ASD. Social cognition and linguistic skills have also often been described as atypical or delayed in children with ADHD. ADHD has been associated with impairments in facial emotion and prosody perception (Ibáñez et al., 2011; Uekermann et al., 2010). An important question is whether these difficulties are present from the onset, or a secondary consequence of atypical social interaction arising from frequent conduct problems. Relevant to this question and to our review, automatic facial mimicry in response to emotional expressions appears typical in 6–7-year olds with ADHD (Deschamps, Munsters, Kenemans, Schutter, & Matthys, 2014). Intriguingly, studies have failed to establish impairments in establishing secure attachment in ASD (Rutgers, Bakermans-Kranenburg, van Ijzendoorn, & van Berckelaer-Onnes, 2004), while insecure attachment has been frequently associated with ADHD (Storebo, Rasmussen, & Simonsen, 2013).

Language delay has also been described in children with ADHD or ADHD symptoms (e.g. Helland, Posserud, Helland, Heimann, & Lundervold, 2012). In a comparative study, pragmatic language difficulties were documented in both children with ASD and with ADHD (Geurts & Embrechts, 2008). Interestingly, a relationship between characteristics of impulsivity and language abilities was found in the ADHD group, suggesting a possible different developmental origin of language impairment in ASD and ADHD. Another study found that general pragmatic abilities, as measured by parent ratings, mediated the relation between ADHD and poor social skills, in this population (Staikova, Gomes, Tartter, McCabe, & Halperin, 2013).

Early ASD. The time course of social and communication development in typical development has been extensively studied, and it is widely accepted that a chain of cascading events lead to typical social integration and social learning. As reviews of this topic in infants at-risk for ASD have recently been published (Jones et al., 2014), here we focus on highlighting representative findings only. Orienting to faces and eyes is commonly reported to be typical during most of the 1st year of life (Elsabbagh, Fernandes, et al. 2013; Elsabbagh, Gliga, et al. 2013; Elsabbagh et al. 2014; Ozonoff et al., 2010; Young, Merin, Rogers, & Ozonoff, 2009), but decreases subsequently (Jones & Klin, 2013; Ozonoff et al., 2010). In a recent, densely sampled longitudinal eye-tracking study, 2-month-old infants who later developed autism looked significantly more toward the eyes than typically developing infants; by 24 months, these effects had reversed (Jones & Klin, 2013). Responses to the ‘still face’ – which may index early social motivation – are also typical at 6 months of age (Rozga et al., 2011; Young et al., 2009). However, low infant positive affect and infant attentiveness to parent, recorded at 12 months during parent–child interaction, relate to 3-year autism outcome (Wan et al., 2013). At 6 to 9 months, event-related potentials (ERP) show less differentiation of faces that shift gaze toward versus away from the viewer in infants with later ASD (Elsabbagh et al., 2012). Impairments in behavioral measures of gaze following become apparent at the beginning of the 2nd year and correlate with measures of autism symptom severity (e.g. Bedford et al., 2012).

Several studies have identified delays in receptive and expressive language by 12 months of age in infants later diagnosed with ASD on standardized and parent-report measures (Landa & Garrett-Mayer, 2006; Mitchell et al., 2006; Zwaigenbaum et al., 2005; but see Hudry et al., 2014 and Talbott, Nelson, & Tager-Flusberg, 2015; for no differences). There may also be more subtle delays in expressive language that are detectable earlier in development; Paul, Fuerst, Ramsay, Chawarska, and Klin (2011)

observed more immature vocalizations (e.g. fewer 'middle' consonant types at 6 months, fewer 'late' consonant types at 9 months, and a lower total number of different consonant types at 12 months) in infants with later symptoms of ASD. Whether these atypicalities indicate general compromised motor development or are an early expression of problems with learning language-specific phonological or prosodic information is unknown.

Early ADHD. Very few studies have examined early social skills in infants with later ADHD. However, disorganized attachment in infants next-born after stillbirth predicts teacher ratings of ADHD in preschool (Pinto, Turton, Hughes, White, & Gillberg, 2006). Speech and language delays have been documented at 9 and 18 months in a retrospective chart review of children with ADHD relative to typically developing controls (Gurevitz et al., 2012). One third of children with later ADHD showed delays in speech development at 9 months, and two thirds by 18 months. One large population cohort prospective study only measured language skills at 36 months of age and found boys with more severe ADHD to be delayed in receptive language (Arnett et al., 2013).

General issues. There is strong evidence that language delays are detectable from at least 12 months in some infants with later ASD (e.g. Zwaigenbaum et al., 2005), and some preliminary evidence that delays may also be apparent in up to two thirds of infants with later ADHD (Gurevitz et al., 2012). Although this is a point of convergence between ASD and ADHD, as language acquisition draws on a variety of skills, different developmental mechanisms may explain poor language in ASD and ADHD. For example, difficulties with understanding social cues more commonly invoked to explain poor word learning in ASD (Gliga, Elsabbagh, Hudry, Charman, & Johnson, 2012). However, using gaze direction for word learning might itself depend on the ability to flexibly switch attention (Schietecatte, Roeyers, & Warreyn, 2012; although see Leekam, López, & Moore, 2000; for a dissociation in children with ASD). Thus, it remains possible that attention difficulties common to ASD and ADHD are responsible for language delays in both these groups, as well as other language impaired populations (Kelly, Walker, & Norbury, 2013). Studying precursors to later language difficulties in both ASD and ADHD, as well as in other developmental disorders will help us to understand the contribution of overlapping or distinct developmental pathways to social interaction and language development (Karmiloff-Smith et al., 2012).

Discussion

We have reviewed several domains that appear to differ in both the early development of children with

ASD and/or ADHD. The following section covers the implications of these findings for existing developmental models of ASD and ADHD.

Are there syndrome-specific infant markers?

One of the motivating questions for this review is whether infant markers are specific to later diagnostic or dimensional outcome. One significant limitation to the current literature is that most studies either examine group differences in infant features between children with different later diagnoses; or continuous relations between infant features and later symptomatology. Few studies examine whether early features represent markers or predictors at the individual level (see Table 1). This limits our current understanding of the specificity and sensitivity of early features to later diagnosis. Further, to identify syndrome-specific predictors requires studies that involve infants with later ASD, ADHD, and comorbid outcomes, receiving a common battery of infant and outcome measures; few of these studies have been conducted. Even here, further evidence would be required to demonstrate specificity with regard to other commonly comorbid conditions such as anxiety. Nevertheless, our review highlighted a few candidate markers worthy of further investigation: at least some children with ADHD show particularly early attainment of motor milestones (Gurevitz et al., 2012), while motor delays are more commonly reported in ASD (Landa & Garrett-Mayer, 2006; LeBarton & Iverson, 2013; Ozonoff et al., 2010); there are reports of reduced head circumference in ADHD versus early overgrowth in ASD (but see Rommelse et al., 2011); early temperament ratings suggest better adaptability and more approach in 6-month olds with later ASD (Del Rosario et al., 2014), but lower adaptability and lower approach in 6-month olds with later ADHD (Arnett et al., 2013); and disengagement of attention is problematic in ASD (e.g. Elsabbagh, Fernandes, et al. 2013; Elsabbagh, Gliga, et al. 2013), while difficulties in maintaining attention may predict later ADHD symptomatology (e.g. Lawson & Ruff, 2004a). However, assessment of behavioral skills has usually been made under conditions that are not directly comparable. To better establish these candidates for specific markers, future prospective studies of infants that later develop ASD and/or ADHD symptoms will require us to use identical experimental paradigms.

Are there common markers across different syndromes?

While the criteria for establishing common infant markers are less stringent than those described above (as only one instance of a common predictor need be observed in the two conditions), establishing that this is true across multiple measures will require consid-

erable further evidence. Reviewing the current body of evidence from studies of early ASD and ADHD suggests that some commonalities can be established, such as similarities in the time course of language milestones. However, cross-study comparisons relying on different measures do not allow us to determine whether there may be differences in the degree or nature of the delay experienced by infants who go on to ASD or ADHD. This is critical to evaluating models in which ASD and ADHD represent different aspects of an underlying continuum of impairment (Van der Meer et al., 2012). In addition, as no studies have yet examined predictors of comorbidity, it may be that early language delays appear to be a common feature, but in fact relate to later symptoms of autism in children with ADHD diagnoses (Figure 1A). Further, global assessments of development may not be sufficiently sensitive to inform us about common underlying mechanisms.

There are a number of reasons why common markers across different outcomes may be observed: (1) ADHD and ASD are actually two manifestations of a common underlying disorder, and therefore the earliest emerging markers are common, (2) ASD and ADHD share a common endophenotype(s), in addition to factors specific to each condition, (3) syndrome-specific initial developmental atypicalities lead to common compensatory mechanisms of brain adaptation. We now consider each of these possibilities in the light of the evidence we have reviewed on early predictors, and discuss the extent to which they can potentially be teased apart by evidence from the infancy period.

1. ASD and ADHD really a common underlying disorder?

As mentioned in the Introduction, despite the different diagnostic categories, some experts have proposed that these syndromes could be manifestations of a common underlying disorder (Van der Meer et al., 2012). From this perspective, finding common early predictors would be expected, and we would predict little success in the search for syndrome-specific infant predictors. Another possibility is that ADHD may represent a milder form of the same underlying condition as ASD (Van der Meer et al., 2012). From our review of existing evidence, differences in measures such as head circumference or motor skills seem incompatible with identical early profiles.

2. Do ASD and ADHD share a subset of common endophenotypes?

A second model proposes that while ASD and ADHD are distinct syndromes, they share one or more endophenotypes (Gottesman & Gould, 2003). This was inspired by finding similar performance in, for example, measures of empathy, sensory responsiveness, or emotion regulation (reviewed in Rommelse et al., 2011), but also by twin studies showing that more children with one condition show *features* of the

other condition than show complete comorbidity (Ronald, Larsson, Anckarster, & Lichtenstein, 2014). Under this model, we predict longitudinal continuity for the specific domains that are underpinned by common endophenotypes. For example, early life motor milestones being delayed for some individuals who go on to both conditions could be interpreted as reflecting a common underlying endophenotype. Finding common endophenotypes will be helped by dimensional approaches to ASD and ADHD characterization where early markers for particular symptoms (e.g. inattention or poor joint attention) are assessed across disorders. The level at which the investigation is carried out (molecular, neuronal function, or behavioral) and the degree to which multiple factors are considered, will also determine whether common endophenotypes are observed. For example, it is possible that common genetic factors that act on brain growth are switched on at different time points in prenatal development (by other genetic or environmental factors), leading to either accelerated or reduced growth. Moreover, sleeper effects of earlier mutations have been described, which could lead to delayed manifestations of a disease in adolescence (Korade & Mirnics, 2014).

3. Brain adaptation and common compensatory factors

Under this third scenario (Figure 1C,D), common infant markers of outcome are observed because they reflect common mechanisms of brain adaptation or compensation, in the face of mild but widespread disturbances to early brain function (Johnson, 2012; Johnson et al. in press). As discussed earlier, Johnson (2012) argued good prefrontal EF skills may be a protective factor across several different development disorders (Figure 1D). Under this view, poor EF skills in infants at-risk will tend to be associated with later diagnoses. The reductions in “effortful control” observed in both toddlers who go on to later ASD and ADHD diagnoses are consistent with this proposal, but clearly further work is required. A more radical proposal is that key diagnostic features of ASD, and possibly also ADHD, are primarily manifestations of brain adaptation in the face of poor quality signal processing early in life (Johnson et al. in press; Figure 1C). Under this view, the diagnostic features of ADHD differ from those in ASD by virtue of the time in the life course when the adaption processes begin (happening in ASD before ADHD), and comorbidity is a likely consequence of processes of adaptation being engaged over a longer period.

Recommendations for future work Causes or consequences

Traditionally, when studying infants at high risk, investigators have typically chosen tasks in infants that are thought to be domain-relevant precursors.

For example, social orienting is assumed to be a necessary precursor skill for more advanced social perception and cognition, and therefore has been a primary target for groups investigating infants at high risk for ASD, while regulatory behaviors are more commonly studied as putative markers for ADHD. The work we have reviewed suggests that the quest for common markers may require stepping away from precursors to antecedents (see Table 1), by which we mean markers that may have little apparent surface similarity to later symptoms and may even be transitory in development. Johnson et al. (in press) propose that a number of symptoms of ASD or ADHD may result from mechanisms of brain adaptation in the face of early disturbances to synaptic function. The resulting adaptations may bear little resemblance to the original atypicality as they represent a whole developing brain's attempts to select an environment that best suits its own capacities. For example, by this view withdrawal from social interactions in toddlers with emerging ASD is a consequence of their inefficient processing of complex spatial-temporal information. The same information processing difficulties, when emerging later in development, may lead to slightly different adaptive responses (e.g. conduct problems instead of social withdrawal). Thus, infant predictors of the efficiency of synaptic connectivity will be better candidate predictors than disorder-relevant markers.

The effect of risk group

The work reviewed above highlights the need to examine the same candidate markers in relation to ASD and ADHD outcomes in a range of cohorts. The vast majority of studies on early ASD have been conducted with infants at high familial risk, but there may be different genetic paths to autism in these cohorts relative to sporadic cases (e.g. Willsey et al., 2013) and this may also be true for ADHD. In addition to forming a critical test of the generalizability of currently identified features of early ASD/ADHD, studying population samples and a range of other risk groups (e.g. prematurity, early environmental exposure, familial risk, single gene mutations) will also allow us to more easily identify broad protective factors (e.g. Johnson, 2012). Further, if behavioral symptoms of ASD and ADHD represent common compensatory responses to a multitude of original risk factors (Johnson et al. in press), one would predict that infant markers that reflect compensatory responses should be observed across multiple risk groups. Thus, we argue that it will be critical to examine which aspects of causal paths to developmental disorders are shared versus distinct in different risk groups.

To better unravel causal factors, studies of infants selected to be at familial or perinatal factor risk (such as prematurity) will also need to be supplemented by studies of infants with de-novo or single gene muta-

tions. Single gene mutations have the obvious advantage that one of the original causal factors is known. However, as the prevalence of ASD and ADHD in children with single gene mutations is rarely 100%, it is important to recognize that pathways to later behavioral traits of ASD or ADHD will be complex. As an example of the potential of studying single gene disorders, a recent study indicated that approximately 25% of individuals with the NF1 mutation meet criteria for ASD, and approximately 50% meet criteria for ADHD (Garg et al., 2013). However, the rate of ADHD was similar in the groups with and without ASD, indicating no statistical association between the two disorders. This raises the intriguing possibility that NF1 mutation impacts neurophysiological mechanisms that act as common risk/protective factors for both ASD and ADHD, revealing the base rate of risk for the two disorders (see also Moreno-De-Luca et al., 2013). Mapping early causal paths to later ASD and ADHD symptoms in infants with NF1 versus infants with other risk factors (e.g. familial risk) may thus allow us to tease out markers that represent the absence of protective factors from those that represent active risk factors for each condition.

Early intervention

A better understanding of common and different causal pathways to ASD/ADHD should allow for more targeted interventions (e.g. directed at social and communication skills, Wallace & Rogers, 2010; vs. directed at attention skills, e.g. Wass, Porayska-Pomsta, & Johnson, 2011). Such interventions may also reveal causal mechanisms in developmental pathways (Green et al., 2013), although it will be important to consider the ethical aspects of providing treatment to individuals who have yet to display developmental difficulties. Parent-mediated interventions may be particularly powerful in early infancy, as parental behavior affects both social-communicative learning (Tamis-LeMonda, Song, Leavell, Kahana-Kalman, & Yoshikawa, 2012) and the development of executive functions (Cuevas et al., 2014). Identifying common protective factors may be particularly important, because interventions that target these factors would be applicable to a broad range of conditions. Further, identifying which early risk markers have cascading consequences and which are simply reflections of the disease process will be critical in determining the most critical intervention targets. For example, transient delays in achieving motor milestones could contribute to later sociocommunicative delays because infants are not able to actively influence their social environment to the same extent; alternatively, motor delays may simply reflect an immature nervous system. In the former case, specifically treating early motor delays may bring benefits for social communication skills; this would not be true of the latter case.

Outcome measurement issues

Evaluating the degree to which particular markers are specific or common to later ASD and ADHD will require comparable use of outcome assessments. Most current studies examine either categorical outcome of ASD, or dimensional measures of ADHD symptoms; using both measures for each disorder will increase comparability and contribute to the debate about the categorical versus dimensional nature of diagnosis (e.g. Coghill & Sonuga-Barke, 2012). Further, examining whether there are gender differences in the relation between risk markers and later ASD or ADHD will be important, as both ASD and ADHD are more common in males than females and the mechanisms that lead to this sexual dimorphism are only partly understood. Finally, long-term follow-up of samples past early childhood will be critical, as there is considerable variability in the later course of both ASD and ADHD. Longitudinal studies of infants at risk for ASD and ADHD will be required to adopt a long-term approach to understand how early markers related to developmental trajectories across the life course.

Conclusions

Taken overall, our review of infant precursors for the later emergence of ASD or ADHD has yielded more evidence for commonalities in the affected domains than syndrome-specific early features. However, we note that the criteria for establishing that a marker is unique to a syndrome are challenging, and further that there are multiple possible explanations for why different diagnostic syndromes may share common early life predictors. We conclude that future work needs to examine the relation between infant predictors and ASD and ADHD

symptomology in the same cohorts, with both categorical and dimensional outcome measures. Models should test whether apparently similar early symptoms reflect the same or different underlying causal mechanisms, and whether apparently different patterns of early atypicality (e.g. motor milestones, head circumference) support strong conclusions about qualitatively different causal paths. Examining these domains in children with different patterns of co-occurrence will also be critical. Finally, realizing the potential of this field to provide transformative clinical change requires an increased focus on laying the translational foundations for the development of new intervention paradigms.

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Key points

- Autism and ADHD are neurodevelopmental disorders that commonly co-occur, and share genetic and environmental risk factors.
- Understanding shared and distinct causal pathways to ASD and ADHD requires prospective longitudinal studies of infants who later develop the two conditions.
- Our review reveals developmental commonalities in domains like early motor delays and atypicalities in attention, while early temperament and head circumference may reflect more condition-specific disruptions.
- Future research should assess infant neurocognitive functioning in relation to both later categorical diagnosis of different conditions, and to dimensional assessments of a range of symptom domains within the same cohort.
- Clinicians should be aware that early delays can be a red flag for multiple later disorders; this may indicate a developmental window for intervention that could ameliorate later symptoms of a range of conditions.
- To increase translatability, research should move from the study of early symptom-related markers to examining causal antecedents linked to underlying alterations in early brain function.

Note

1. These rates may be underestimates since many children would receive a diagnosis of ADHD beyond 7 years of age and also because clinicians often refrain from giving a dual diagnosis.

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